Section 112 Rejections

In response to this rejection, Claims 2-6 have been amended to identify formula I.

Claim Objections

Claims 10-14 have been amended to limit the compound to stereoisomeric form R. New claim 15-19 are similar to claims 10-14 except the compounds claimed are limited to stereoisomeric form S.

Section 103 Rejections

The Examiner has alleged that the claimed compound, 1α-hydroxyvitamin D_5, is prima facie obvious because the references teach a generic group of vitamin D derivatives of which 1α-hydroxyvitamin D_5 is a "specific species". Furthermore, the Examiner alleges that "an ordinary artisan would have the reasonable expectation that any of the species of the genus would have similar properties and, thus, the same use as the genus as a whole." The Examiner appears to have taken the position that structural similarity gives rise to the expectation that the compounds disclosed in the cited references have properties similar to the claimed compound. However, as will now be explained, this is certainly not the case. While the claimed compound may be "chemically obvious" in the sense that one or more of the cited references disclose a genus compound of which Applicants' Vitamin D5 compound is a specific species, the unexpected properties of 1α-hydroxyvitamin D_5 not in fact possessed by its Vitamin D analogues rebuts a finding of

nonobviousness based only on similarity of structure.

It is well established that patentability of a chemical compound is not to be determined on the basis of structure alone, and that "from the standpoint of patent law, a compound and all of its properties are inseparable." In re Papesch, 137 U.S.P.Q. 43 (CCPA 1963). On this same topic the Federal Circuit has stated that "generalization should be avoided insofar as specific chemical structures are alleged to be prima facie obvious one from the other." In re Grabiak, 226 U.S.P.Q. 870, 557-58 (Fed. Cir. 1985). Under what is now referred to as the Papesch doctrine, a prima facie case of obviousness based on structural similarity may be rebutted by evidence that the claimed compound has unexpected properties not in fact possessed by the structurally similar prior art compound(s). Furthermore, these differences in properties can include "significant differences in degree of the same property amounting to a marked superiority." In re Hoch, 166 U.S.P.Q. 406 (CCPA 1970).

That 1α-hydroxyvitamin D_5 is part of a homologous series of compounds does not necessarily mean that it exhibits the same properties as the rest of the compounds in the series. It does not. As will now be described, 1α-hydroxyvitamin D_5 has unexpected beneficial properties not possessed by other vitamin D analogues.

First and foremost, 1α-hydroxyvitamin D_5 exhibits lower calcemic activity compared to its analogues, which makes it particularly valuable for use in mammary tumorigenesis

prevention. High calcemic activity is a contraindication for use of vitamin D compounds for non-bone related medical indications (such as use in mammary tumorigenesis prevention) where increased calcium levels are harmful. While its closest Vitamin D analogues increase serum calcium, making them poor candidates for mammary tumorigenesis prevention, 1α-hydroxyvitamin D_5 exhibits relatively lower calcemic activity.

The compound most closely related to 1α-hydroxyvitamin D_5 is perhaps 1α-hydroxyvitamin D_4 (see Knutson et al. U.S. Patent No. 5,488,120, attached hereto and in the Supplemental Information Disclosure Statement filed concurrently herewith). The difference in molecular structure between 1α-hydroxyvitamin D_5 and 1α-hydroxyvitamin D_4 is that 1α-hydroxyvitamin D_5 has a C24 ethyl group whereas 1α-hydroxyvitamin D_4 has a C24 methyl group. Yet the Knutson '120 patent teaches that 1α-hydroxyvitamin D_4 is useful for the treatment of disorders of calcium metabolism by increasing serum calcium (see, inter alia, Knutson '120 at col. 6, lines 29-30). Such a result would lead one skilled in the art to expect 1α-hydroxyvitamin D_5 to have a similar effect, whereas, surprisingly, it does not.

A comparison of the data in Knutson '120 to the present application bears out this unexpected difference in calcemic activity. For example, Table 1 of Knutson '120 indicates that 1α-hydroxyvitamin D_4, when administered to rats at a dosage of 0.042 mg/kg/day, causes an increase in serum calcium of 7.1 +/- 0.45 mg/100 mL compared to only 6.0 +/- 0.63 mg/100 mL for 1α-

hydroxyvitamin D_5 (see Table 1 of application). Thus, at a dose of 0.042 mg/kg/day, 1α-hydroxyvitamin D_4 is about 18% more calcemic. At 0.25 mg/kg/day the difference is even greater: 1α-hydroxyvitamin D_4 is about 47% more calcemic that 1α-hydroxyvitamin D_5.

Thus, based on the Knutson '120 patent, one would predict similar calcemic activity for the heretofore unknown compound 1α-hydroxyvitamin D_5. This expectation is clearly erroneous as indicated by the data in Table 1 of the specification.

Because its most closely related analog exhibits high calcemic activity, it would not have been obvious to one skilled in the art at the time of the present application to attempt to synthesize 1α-hydroxyvitamin D_5 for possible use in treating mammary neoplasia. Yet, due to its surprisingly low calcemic activity, 1α-hydroxyvitamin D_5 can be administered at sufficiently high levels to act as an antiproliferative and cell differentiating substance when acting on mammary tumor cells without significantly affecting calcium metabolism. The attached Declaration of John E. Nelson, M.D., most recently a Clinical Pharmacologist with Evanston Hospital in Evanston, Illinois, establishes that its low calcemic activity makes 1α-hydroxyvitamin D_5 a novel and promising candidate for cancer chemotherapy and prevention.

In summary, 1α-hydroxyvitamin D_5 exhibits anti-cancer properties superior to the 1α-hydroxyvitamin D_4 compound disclosed in Knutson '120. A person of ordinary skill in the art

would not have the reasonable expectation that 1α-hydroxyvitamin D_5 would be less calcemic that 1α-hydroxyvitamin D_4 and 1,24-dihydroxy D_4 even though these two compounds belong to the same vitamin D genus. The fact that 1α-hydroxyvitamin D_5 has unexpected properties not in fact possessed by structurally similar compounds supports a finding that the present invention is neither anticipated by nor rendered obvious in view of the prior art compounds.

Because of its superior properties over other Vitamin D analogues, Applicants continue to study 1α-hydroxyvitamin D_5. The attached Declaration of Rajendra G. Mehta, one of the inventors of 1α-hydroxyvitamin D_5, describes the effect of 1α-hydroxyvitamin D_5 on body weight and serum calcium level in rats. The data shows that 1α-hydroxyvitamin D_5 continues to be a promising candidate for cancer prevention and therapy.

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The enormous number of known organic compounds has given rise to a situation in which absolutely unique and unknown compounds (as opposed to homologs, analogs or isomers) is rare. In light of this circumstance, some courts have long been of the view that patentability is not determined on the basis of structural obviousness alone. Rather, obvious molecular modification coupled with a showing of novel properties or superiority of known properties can establish patentability. Commissioner of Patents v. Deutsche Gold-und-Silber Scheideanstalt Vormals Roessler, 397 F. 2d 656, 663, 157 U.S.P.Q.

549, 554 (D.C. Cir. 1968). The present compound is patentable because none of the prior art references disclose the exact 1α-hydroxyvitamin D_5 compound claimed here and because 1α-hydroxyvitamin D_5 exhibits novel properties that make it superior to its Vitamin D analogs.

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As will now be discussed, 1α-hydroxyvitamin D_5 exhibits unexpected properties over the compounds actually synthesized and tested in the references cited by the Examiner.

Holick et al. '538

Applicants do not dispute that Holick et al. '538 discloses a genus encompassing the particular compounds in Claims 1-6 and 10-19. However, Applicants respectfully submit that 1α-hydroxyvitamin D_5 is not obvious in view of Holick '538 because, as discussed above, 1α-hydroxyvitamin D_5 exhibits properties that make it superior to the Vitamin D compound tested in Holick '538.

Holick '538 is directed to a "Method of Treating Periodontal Disease." Holick describes the physiological action of naturally occurring Vitamin D compounds and claims their use as his invention. Holick hypothesizes that a panoply of modifications to the structure of a naturally occurring vitamin will result in compounds having clinical therapeutic efficacy with an acceptable toxicological profile. However, generalizing that compounds of similar structure will have similar properties is not a very reliable predictor. As noted above, 1α-hydroxyvitamin D_5 exhibits a very different therapeutic/toxicologic profile than

its Vitamin D analogs.

Applicants respectfully disagree with Examiner's statement that "an ordinary artisan would have the reasonable expectation that any of the species of the genus would have similar properties and, thus, the same use as the genus as a whole." The properties taught by Holick for naturally occurring Vitamin D (treating periodontal disease) are different from the properties exhibited by Applicants 1α-hydroxyvitamin D_5 compound (preventing mammary lesion formation and low calcemic activity).

Unlike Applicants, Holick has not actually synthesized any Vitamin D compounds. Consequently, Holick does not teach any practical and reproducible routes of synthesis of any Vitamin D compound, much less 1α-hydroxyvitamin D_5. Holick's hypothesis that a group of compounds which have not yet been synthesized and for which practical and reproducible routes of synthesis are as yet unknown should not be held to render obvious Applicants' novel Vitamin D5 compound or its method of synthesis.

Holick et al. '643

Here Holick claims as his invention a "Method of Treating Psoriasis." Holick describes the physiologic activity of naturally occurring Vitamin D compounds and claims their use as his invention. As in the '538 patent, Holick hypothesizes that a panoply of modifications to the structure of naturally occurring Vitamin D will result in compounds having clinical therapeutic activity with an acceptable toxicologic profile. However, generalizing that compounds of similar structure will have

similar properties is not a very reliable predictor. As noted above, 1α-hydroxyvitamin D_5 exhibits a very different therapeutic/toxicologic profile than its Vitamin D analogs.

Again Applicants disagree with Examiner's statement that "an ordinary artisan would have the reasonable expectation that any of the species of the genus would have similar properties and, thus, the same use as the genus as a whole." The properties taught by Holick '643 for naturally occurring Vitamin D (treating psoriasis) are different from the properties exhibited by Applicants 1α-hydroxyvitamin D_5 compound (preventing mammary lesion formation and low calcemic activity). For instance, Holick alludes to the use of vitamin D analogues as an effective method of therapy for diseases involving calcium, phosphorus and bone metabolism problems. Col. 3, lines 11-15. In other words, Holick teaches that vitamin D analogues can be used to increase serum calcium. In view of this statement, one skilled in the art would not expect 1α-hydroxyvitamin D_5 to exhibit low calcemic activity. The fact that it does, supports a finding that 1α-hydroxyvitamin D_5 is not obvious in view of Holick.

Bishop et al. '429

Bishop claims as his invention a "Method of Treating Prostatic Diseases Using Active Vitamin D Analogues." Bishop describes clinical studies performed on patients with advanced androgen-independent prostate cancer using 1α,24-dihydroxyvitamin D_2 and 1α-hydroxyvitamin D_2. The results indicate stable disease or partial or complete remission of the disease. Bishop

incorporates other references for teaching how to make these compounds. Significantly, Bishop does not provide any data for 1α-hydroxyvitamin D_5. This is because, among other reasons, it had never been synthesized until Applicants successfully did so.

Gulbrandsen et al. '790

Gulbrandsen claims as his invention a "Method of Treating and Preventing Myocardial Failure." Gulbrandsen describes the physiologic action of naturally occurring Vitamin D compounds and claims their use as his invention. Gulbrandsen hypothesizes that a panoply of modifications to the structure of a naturally occurring vitamin will result in compounds having clinical therapeutic efficacy and an acceptable toxicologic profile. Applicants once again note that generalizing that compounds of similar structure will have similar properties is not a very reliable predictor. As noted above, 1α-hydroxyvitamin D_5 exhibits a very different therapeutic/toxicologic profile than its Vitamin D analogs.

Other Prior Art

The following two patents were disclosed by Applicants in a Supplemental IDS filed concurrently herewith.

Knutson et al. U.S. Patent No. 5,488,120 teaches and claims 1α-hydroxyvitamin D_4. The patent teaches that this novel compound is useful for disorders of calcium metabolism. A method of synthesis is provided.

Moriarty et al. U.S. Patent No. 5,869,472 teaches and claims a method of synthesizing 1α-hydroxyvitamin D_2.

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Summary

For the foregoing reasons, Applicants submit that Claims 1-6 and 10-19 are in condition for allowance. Applicants request an early and favorable ruling allowing same.

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The Examiner is invited to telephone applicant's undersigned attorney if any unresolved matters remain.

Respectfully submitted,

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